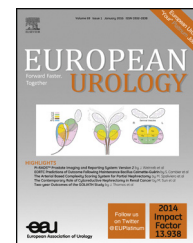


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## Platinum Priority – Prostate Cancer

Editorial by Michael Kolinsky and Johann S. de Bono on pp. 841–843 of this issue

# Pharmacokinetics, Antitumor Activity, and Safety of ODM-201 in Patients with Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer: An Open-label Phase 1 Study

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## Abstract

**Background:** ODM-201 is a novel second-generation androgen receptor inhibitor for the treatment of metastatic castration-resistant prostate cancer (mCRPC).

**Objective:** To evaluate the pharmacokinetics of ODM-201 tablet products and preliminary long-term safety, tolerability, and antitumor activity of ODM-201 in chemotherapy-naïve men with mCRPC.

**Design, setting, and participants:** Thirty patients were enrolled in this open-label phase 1 trial. Patients received a single 600-mg dose of ODM-201 in capsules with food and one 600-mg dose of ODM-201 tablet product (TabA or TabB) with food and in the fasted state in a random order. In the extension, patients received 600 mg twice daily ODM-201 taken with food in capsules.

**Outcome measurements and statistical analysis:** We analyzed the pharmacokinetics of ODM-201 tablet formulations. Safety and tolerability were assessed until disease progression or an intolerable adverse event (AE). Antitumor activity was assessed by prostate-specific antigen (PSA) levels and imaging.

**Results and limitations:** The capsule:TabA ratio of area under the concentration-time curve from time zero to the last sample at 48 h was 1.06 (90% confidence interval [CI], 0.91–1.24); the capsule:TabB ratio was 0.97 (90% CI, 0.82–1.14). At week 12, 25 of 30 patients (83%) had a PSA response ( $\geq 50\%$  reduction from baseline). Median time to radiographic progression was 66 wk (95% CI, 41–79). Most common AEs were fatigue ( $n = 4$  [13%]) and nausea ( $n = 4$  [13%]).

**Conclusions:** The study showed that the tablet formulation of ODM-201 had similar pharmacokinetics compared with the capsule. Treatment with a 600-mg twice daily dose of ODM-201 provided anticancer activity and was well tolerated in men with chemotherapy-naïve mCRPC.

**Patient summary:** The findings of this study showed that ODM-201 is well tolerated and provided antitumor activity in chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (mCRPC) and that the 300-mg tablet formulation can be used in further clinical studies. A phase 3 trial with ODM-201 600 mg twice daily in patients with non-mCRPC is ongoing.

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## 1. Introduction

The initial treatment for metastatic prostate cancer (PCa) is androgen deprivation therapy, using either surgical or chemical castration [1,2]. Although this approach usually results in anticancer efficacy [3], most men develop castration-resistant prostate cancer (CRPC) within 2–3 yr. Until recently, chemotherapy with docetaxel was the only proven treatment option for metastatic CRPC (mCRPC); however, with increased understanding of the mechanisms underlying castration resistance, two new hormonal treatments—abiraterone [4] and enzalutamide [5]—were recently licensed in the European Union and United States for pre- and postdocetaxel treatment of mCRPC. Abiraterone is an irreversible inhibitor of the CYP17A enzyme that catalyzes the production of androgens [6]; enzalutamide is a second-generation androgen receptor (AR) antagonist.

Enzalutamide is generally well tolerated but can lead to fatigue [5,7] and an increased risk of seizures. Although the incidence of seizures in enzalutamide trials was low [5,7,8], the risk of seizures in patients with predisposing factors or a history of seizures is not known because such patients were excluded from the trials [9].

ODM-201 is a novel oral second-generation AR inhibitor with a similar mechanism of action to enzalutamide, but structurally distinct, with negligible penetration of the blood–brain barrier in preclinical studies [10]. ODM-201 is a mixture (1:1) of two pharmacologically active diastereomers: ORM-16497 and ORM-16555, which like the major metabolite ORM-15341, have a higher affinity for the AR than enzalutamide [10]. In preclinical studies, ODM-201 significantly inhibited tumor growth in a murine VCap CRPC xenograft model [10]. A phase 1/2 study of ODM-201 (ARADES) in men with mCRPC was published in 2014 and included patients with a history or at risk of seizures [11]. In the dose-escalation part ( $n = 24$ ), doses of 100–900 mg twice daily resulted in no dose-limiting toxicity. In the phase 2 part ( $n = 110$ ), which evaluated doses of 100, 200, and 700 mg twice daily, most patients experienced prostate-specific antigen (PSA) decline. The best PSA response was observed in patients treated with 700 mg twice daily (86%) who had not previously received chemotherapy or CYP17 inhibitors. ODM-201 was well tolerated; >99% of adverse events (AEs) were grade 1–2 [11].

Dosing of ODM-201 in the ARADES study was via 100-mg capsules, necessitating the administration of a large number of capsules in patients on higher doses. Subsequently, two new tablet products were developed, each containing 300 mg ODM-201.

The aims of the current study (ARAFOR) were, in the first component, to evaluate the pharmacokinetics of two tablet products relative to the capsule formulation and to evaluate the effect of food on ODM-201 absorption and, in the second component, to preliminarily assess the long-term safety, tolerability, and antitumor activity of an ODM-201 600 mg twice-daily dose in chemotherapy-naïve patients with mCRPC (NCT01784757).

## 2. Methods

### 2.1. Trial design

This was a two-part multicenter international phase 1 study (Fig. 1A and 1B). The first pharmacokinetic (PK) component was a randomized open-label, two-arm, three-period crossover study. The second part was an open-label extension to assess long-term safety and tolerability. The primary end point in the first component was PK of tablet products compared with capsule formulation and effect of food. The end points in the second component (the extension) were safety and effects on PSA and lesions.

### 2.2. Patients

Patients aged  $\geq 18$  yr were eligible if they had progressive mCRPC, testosterone level  $< 1.7$  nmol/l, an Eastern Cooperative Oncology Group performance status of 0–1, and if they had not received chemotherapy and were asymptomatic or mildly symptomatic. Patients without bilateral orchiectomy had to continue gonadotropin-releasing hormone therapy during the study. Progressive disease was defined as rising PSA (two consecutive increases in PSA levels obtained at least 1 wk apart with the lowest value  $\geq 2$  ng/ml), radiographic disease progression based on modified Response Evaluation Criteria in Solid Tumors (RECIST v.1.1), or two or more new bone lesions. Brain metastases or previous treatment with a second-generation AR antagonist or CYP17 inhibitor were exclusionary.

### 2.3. Ethics

All patients gave written informed consent for participation. The study was approved by an independent ethics committee at each participating center, and the study was conducted according to the principles of the Declaration of Helsinki, Good Clinical Practice, and applicable regulatory requirements.

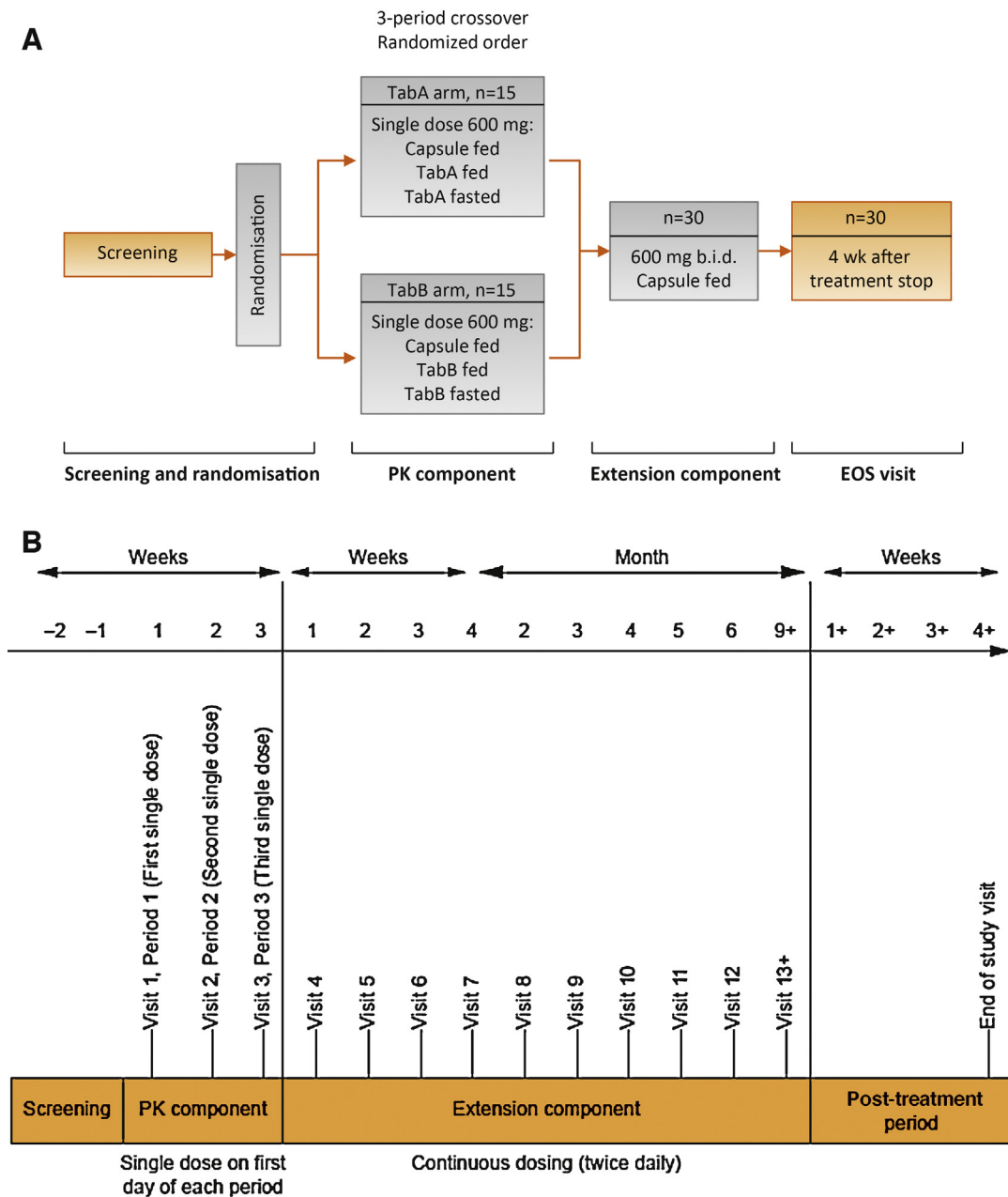
### 2.4. Treatment

During the PK component, patients received a single oral 600-mg dose of the reference ODM-201 capsules ( $6 \times 100$ -mg capsules) with food and a 600-mg dose of either of the two test tablets (TabA or TabB,  $2 \times 300$  mg) in the fed and fasted state. Patients were randomly assigned at a 1:1 ratio to receive TabA or TabB via a electronic data capture system and concealed through a password-protected computer database, and to one of the three treatment sequences according to the trial design. Arm information was blinded. TabA and TabB were conventional immediate-release tablets. TabB was the same formulation as TabA but with a coarser grade of the drug substance. Dosing with food was done 30 min after a standard high-fat high-calorie meal. There was a 7-d washout period between each treatment period.

During the extension, patients were treated with a ODM-201 600-mg capsule taken with food twice daily. Treatment continued until disease progression or an intolerable AE.

### 2.5. Pharmacokinetic assessments

Blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 30, and 48 h postdose in each treatment period. Based on PK of ODM-201 in humans [11], a washout period of 7 d was deemed appropriate to ensure complete clearance of ODM-201 between administrations. Plasma concentrations of ORM-16497 and ORM-16555 (diastereomers of ODM-201) and the major metabolite ORM-15341 were determined



**Fig. 1 – Study overview: (A) trial design; (B) schedule of events.**  
b.i.d. = twice daily; EOS = end of study; PK = pharmacokinetic; TabA = tablet A; TabB = tablet B.

using liquid chromatography with tandem mass spectrometry. The ODM-201 concentration was the sum of the concentrations of the two diastereomers.

The following PK parameters were calculated using Phoenix WinNonlin software (Certara, Princeton, NJ, USA) (noncompartmental method): maximum (peak) plasma concentration ( $C_{max}$ ), time to reach maximum plasma concentration ( $T_{max}$ ), area under the concentration-time curve from time zero to the last sample at 48 h ( $AUC_{0-48}$ ), area under the concentration-time curve from time zero to infinity ( $AUC_{\infty}$ ), and terminal elimination half-life ( $t_{1/2}$ ). The primary parameters were  $C_{max}$ ,  $T_{max}$ , and  $AUC_t$ . PK parameters were calculated for TabA and TabB after administrations at fed and fasted state, and separately for capsule in arms A and B.

## 2.6. Antitumor activity assessments

Disease progression was assessed by changes in PSA and soft tissue and bone. A minimum treatment period of 12 wk was required before PSA progression could be declared.

Computed tomography or magnetic resonance imaging of the chest, abdomen, and pelvis were performed at baseline and every 3 mo to assess soft tissue lesions; response was evaluated using RECIST v.1.1 criteria, with the exception of lymph node lesions, which had to be  $\geq 2$  cm in diameter. Radionuclide bone scans were performed at baseline and every 3 mo. Progression in bone was assessed by Prostate Cancer Working Group (PCWG2) criteria [12]. PSA was analyzed centrally every 4 wk until 9 mo and every 3 mo thereafter. Time to PSA progression was

defined according to PCWG2, that is,  $\geq 25\%$  increase in PSA and an absolute increase  $\geq 2$  ng/ml from nadir as confirmed by an additional PSA performed  $\geq 3$  wk later. Baseline PSA was defined as PSA value obtained before the first dosing in the PK component.

### 2.7. Safety and tolerability

AEs were graded by the National Cancer Institute of Common Terminology Criteria for Adverse Events (v.4.03). Laboratory assessments (hematology, serum chemistry, and urinalysis) were conducted at baseline, every 4 wk until 9 mo, and every 3 mo thereafter.

### 2.8. Statistical analysis

The safety population was defined as all patients who took at least one dose of ODM-201, and the PK population as all patients who received treatment and had no major protocol violations that would compromise reliable determination of PK parameters. The safety and intention-to-treat (ITT) populations were the same. Efficacy is reported for the ITT population. Analyses were performed using data obtained up to the cut-off date of October 31, 2014.

Log-transformed PK parameters ( $C_{max}$ ,  $T_{max}$ , and  $AUC_t$ ) were analyzed using analysis of variance with treatment (test product and fed/fasted state), sequence, and period as fixed effects and patient nested in sequence as a random effect. The PK of TabA and TabB relative to the capsule were evaluated according to the ratio of the geometric means (and two-sided 90% confidence interval [CI]) of the  $AUC$ . The effect of food on the PK of ODM-201 in the TabA and TabB formulations was also evaluated according to the geometric means and two-sided 90% CI. The Wilcoxon signed rank test was used to analyze the  $T_{max}$  and testosterone data and descriptive statistics for the  $t_{1/2}$  data.

The planned sample size for the PK component was 30 patients (15 in the TabA arm and 15 in the TabB arm). The sample size was based on interpatient coefficient of variation of 30% and an inpatient correlation coefficient of 0.35, allowing the 90% CIs to be within 0.8 R and 1.25 R, where R was the point estimate of ratios of  $AUC$  or  $C_{max}$ .

All measurements in the extension were summarized using descriptive statistics. Time to PSA progression and radiographic progression and time on treatment to discontinuation were defined using Kaplan-Meier estimates.

## 3. Results

From March 2013 to July 2013, 30 patients with CRPC in Finland, France, and Latvia were enrolled. All patients completed the PK component and entered the extension. By October 31, 2014, there were 10 ongoing patients in the study. The median reporting period for AEs was 15.3 mo (95% CI, 9.7, not reported [NR]).

The safety and ITT populations were the same comprising 30 patients. The PK population comprised 28 patients in periods 1 and 2, and 29 patients in period 3.

### 3.1. Baseline characteristics

Table 1 summarizes the baseline characteristics.

### 3.2. Pharmacokinetics component

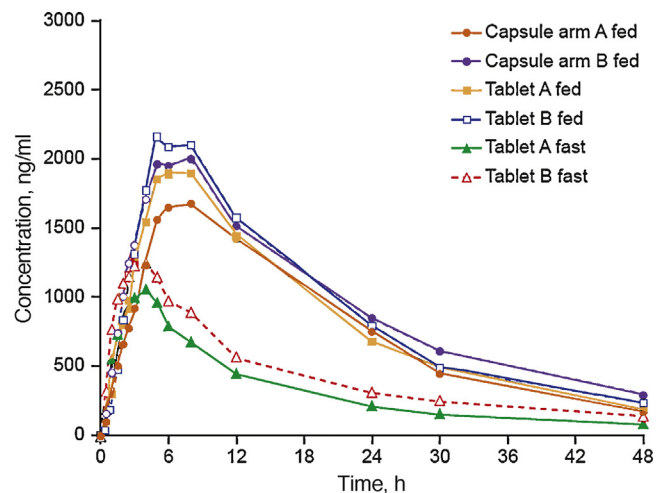
The tablet and capsule formulations provided similar plasma ODM-201 concentrations over time following single

**Table 1 – Baseline characteristics**

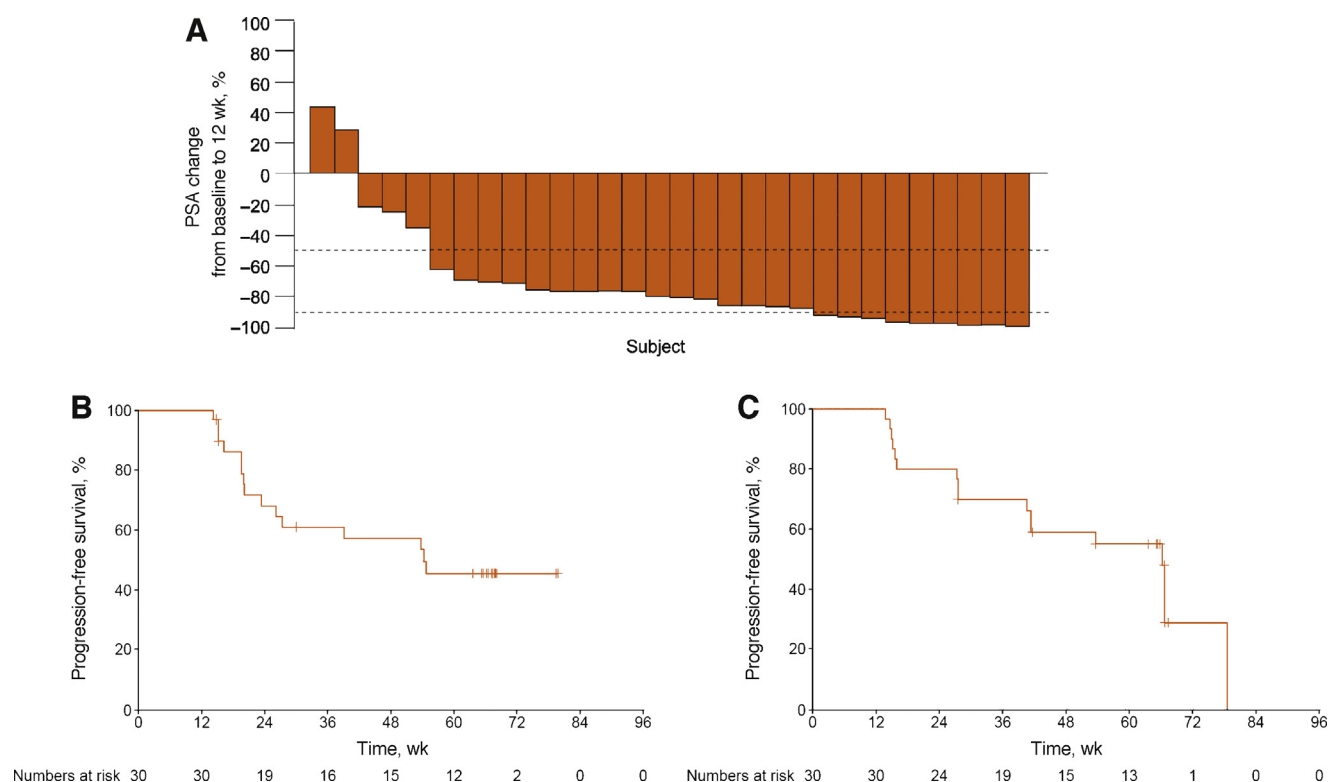
	Total (n = 30)
Age, yr	
Median	68
Q1–Q3	65–71
Race, n (%)	
White	30 (100)
BMI, kg/m <sup>2</sup>	
Median	28.5
Q1–Q3	27.0–30.9
PSA, $\mu$ g/l	
Median	18.2
Q1–Q3	8.2–53.5
Time from initial diagnosis to first dose, mo	
Median	39
Q1–Q3	22–80
Initial treatment of primary tumor, n (%)	
Chemical castration	16 (53)
First-generation antiandrogen	1 (3)
Prostatectomy	4 (13)
Radiotherapy	9 (30)
Prior therapy, n (%)	
LHRH agonist or antagonist	30 (100)
Radiotherapy	17 (57)
First-generation antiandrogen	22 (73)
Systemic corticosteroids	1 (3)
Bone agents	1 (3)
Estrogens	1 (3)
ECOG status, n (%)	
0	20 (67)
1	10 (33)
Disease localization at screening, n (%)	
Bone only	14 (47)
Soft tissue only	3 (10)
Bone and soft tissue	13 (43)
Visceral	3 (10)

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; LHRH = luteinizing hormone-releasing hormone; PSA = prostate-specific antigen; Q1 = 25th quartile; Q3 = 75th quartile.

dosing (Fig. 2). The capsule:TabA ratio of  $AUC_{0-48}$  was 1.06 (90% CI, 0.91–1.24); the capsule:TabB ratio was 0.97 (90% CI, 0.82–1.14). The ratios of  $C_{max}$  were 1.16 (90% CI, 0.99–1.36) and 1.00 (90% CI, 0.86–1.15) for TabA and TabB, respectively. Absorption was slower and plasma exposure



**Fig. 2 – Plasma concentration-time curve for ODM-201 following single-dose administration of capsule, tablet A, and tablet B.**



**Fig. 3 – (A) Percentage change in prostate-specific antigen (PSA) at 12 wk compared with baseline, (B) time to PSA progression by Prostate Cancer Working Group 2 criterion, and (C) time to radiographic progression. PSA = prostate-specific antigen.**

was about twofold greater when dosing with food compared with the fasting state (Supplementary Table 1). Median  $T_{max}$  was 5–6 h in the fed state and about 4 h in the fasting state.  $C_{max}$ ,  $AUC_t$ , and  $AUC_{\infty}$  were approximately twofold greater in the fed state compared with the fasting state.

Median  $T_{max}$  for ODM-201 and the metabolite, ORM-15341, were similar. Mean metabolite-to-parent ratios were similar for the capsule and tablets and were not affected by food ( $C_{max}$ : 1.5–1.8;  $AUC$ : 1.4–1.7). Similar to the effect on ODM-201, food increased the  $C_{max}$ ,  $AUC_t$ , and  $AUC_{\infty}$  of ORM-15341 approximately twofold compared with the fasted state. Food had no effect on the diastereomer ratio.

### 3.3. Extension component: antitumor activity and safety

All 30 patients completed the first 12 wk in the extension. At 12 wk the PSA response rate (PSA decrease from baseline  $\geq 50\%$ ) was 83% (25 of 30); of these patients, 30% (9 of 30) had a PSA reduction  $\geq 90\%$  (Fig. 3A). The median time to PSA progression was 54 wk (95% CI, 23–NR) (Fig. 3B). Table 2 summarizes the soft tissue responses and bone results at 12 wk. The median time to radiographic progression was 66 wk (95% CI, 41–79) (Fig. 3C).

Median serum testosterone level at 12 wk was lower than at baseline (0.60 nmol/l and 0.80 nmol/l, respectively;  $p = 0.5$ ).

A total of 22 of 30 patients (73%) reported AEs; most were grade 1–2 (114 of 125 [91%]). The most common AEs were fatigue (all grade 1) in four patients (13%) and nausea (grade

**Table 2 – Soft tissue and bone imaging results at 12 wk**

Response	Category	n (%)
No. of patients with soft tissue evaluable	–	21 (100)
RECIST response	CR	2 (10)
	PR	4 (19)
	SD	13 (62)
	PD	2 (10)
No. of patients evaluable for bone scan	–	27 (100)
Bone	SD	21 (78)
	PD	6 (22)

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

1–3) in four patients (13%) (Table 3). Events in six patients (20%) were considered by the investigator to be related to ODM-201: fatigue, decreased appetite, headache, abdominal pain, solar dermatitis, tinnitus, and dysgeusia. All treatment-related AEs were grade 1. No dose reductions were made. One patient (3.3%) died because of progression of PCA, and two patients (6.7%) discontinued due to an AE (neuroendocrine carcinoma and respiratory failure). None of the events were considered by the investigator to be related to ODM-201. No seizures were reported.

## 4. Discussion

Results of this study showed that ODM-201 was well tolerated and demonstrated anticancer activity in men with mCRPC.



**Table 3 – Adverse events occurring in >5% of patients by grade (safety population n = 30)**

Adverse event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Total n (%)
Nausea	3 (10)	1 (3)	1 (3)	4 (13)
Fatigue	4 (13)	0	0	4 (13)
Bone pain	1 (3)	2 (7)	1 (3)	3 (10)
Abdominal pain	3 (10)	0	0	3 (10)
Back pain	0	2 (7)	1 (3)	3 (10)
Diarrhea	2 (7)	1 (3)	0	3 (10)
Hematuria	2 (7)	1 (3)	0	3 (10)
Erysipelas	2 (7)	1 (3)	0	2 (7)
Pain in extremity	2 (7)	1 (3)	0	2 (7)
Cough	2 (7)	0	0	2 (7)
Dysuria	2 (7)	0	0	2 (7)
Headache	2 (7)	0	0	2 (7)
Hypertension	0	2 (7)	0	2 (7)
Influenza	2 (7)	0	0	2 (7)
Rhinorrhea	2 (7)	0	0	2 (7)
Rib fracture	2 (7)	0	0	2 (7)
Skin ulcer	2 (7)	0	0	2 (7)
Solar dermatitis	2 (7)	0	0	2 (7)

In the fed state, the pharmacokinetics of 600 mg ODM-201 in the two tablet and capsule formulations was similar and absorption was approximately twofold greater compared with the fasted state. These data suggest the tablet formulation taken with food would be suitable for further investigation in phase 3 studies and can reduce the dosing burden on patients.

Antitumor activity was shown by significant PSA reductions. The soft tissue and bone lesion data, as well as time to PSA progression and radiographic progression, provided evidence of antitumor activity of ODM-201. The PSA response ( $\geq 50\%$  decrease) at 12 wk was 83%, similar to the PSA response of 86% in the ARADES study [11] observed in chemotherapy-naïve patients at 700 mg twice daily. The median time to PSA progression was 55 wk; the median time to radiographic progression was 66 wk.

No statistically significant changes ( $p = 0.5$ ) were observed in median serum testosterone level between baseline and week 12, suggesting negligible brain penetration of ODM-201 and lack of effect on the hypothalamic-pituitary-gonadal axis.

ODM-201 was well tolerated in this study. Similar to the ARADES study [11], most AEs were grade 1–2, all treatment-emergent AEs were grade 1, and no dose reductions were required for any patient. The frequency of AEs commonly reported in patients treated with second-generation AR inhibitors was low, similar to or lower than the AE rate reported by patients in the placebo arm of a phase 3 trial with a comparable population of patients with chemotherapy-naïve mCRPC [7].

Preclinical studies in mice and rats have shown negligible penetration of ODM-201 through the blood–brain barrier [10], and therefore it is not expected to increase the risk of seizures. In contrast, other recently developed second-generation AR inhibitors, enzalutamide and AR-509, were shown to cross the blood–brain barrier in preclinical in vivo models, potentially increasing the risk of seizures by inhibiting  $\gamma$ -aminobutyric acid-gated chloride channels in

the brain [13,14]. Patients with a history of seizures or any predisposing conditions were excluded from the phase 1/2 and 3 trials with enzalutamide [5,7,8] and ARN-509 [15,16], but they were allowed to enter the ARADES study [11] and the current study, where no seizures were reported. The differences in brain penetration between ODM-201 and the other second-generation AR inhibitors is likely related to the unique structure of ODM-201.

## 5. Conclusions

The current study demonstrated that the 600-mg ODM-201 tablet formulation has similar PK to the capsule formulation and that ODM-201 treatment is well tolerated and exhibits antitumor activity in men with CRPC. Based on the results of this study, ODM-201 600 mg is given to patients twice daily as tablets in the randomized placebo-controlled phase 3 study ARAMIS, in men with high-risk non-mCRPC to evaluate the effect of ODM-201 on metastasis-free survival.

Interim data presented at the Genitourinary Cancers Symposium, January 30–February 1, 2014, San Francisco, California, and February 26–28, 2015, Orlando, Florida, and at the 29th European Association of Urology Congress, April 11–15, 2014, Stockholm, Sweden.

**Author contributions:** Karim Fizazi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Massard, Tammela, Vuorela, Nykänen, Snapir, Fizazi.

**Acquisition of data:** Massard, Penttinen, Vjaters, Bono, Lietuvietis, Tammela, Fizazi.

**Analysis and interpretation of data:** Massard, Vuorela, Nykänen, Pohjanjousi, Snapir, Fizazi.

**Drafting of the manuscript:** Massard, Penttinen, Vjaters, Bono, Lietuvietis, Tammela, Vuorela, Nykänen, Pohjanjousi, Snapir, Fizazi.

**Critical revision of the manuscript for important intellectual content:** Massard, Penttinen, Vjaters, Bono, Lietuvietis, Tammela, Vuorela, Nykänen, Pohjanjousi, Snapir, Fizazi.

**Statistical analysis:** Pohjanjousi.

**Obtaining funding:** Snapir, Vuorela.

**Administrative, technical, or material support:** Pohjanjousi, Nykänen, Snapir, Vuorela.

**Supervision:** Fizazi, Massard.

**Other (specify):** None.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2015.09.046>.

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